REMARKS/ARGUMENTS

Reconsideration of this application is requested. Claims 1, 3, 4 and 10-17 are in the case.

I. PRIORITY

The Action asserts that claims 1-3 and 6-10 do not properly benefit under 35 U.S.C. §119 and/or 120 from the earlier filing dates of the claimed priority documents because the claims are rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking adequate written description and lacking sufficient enabling disclosure. In response, and without conceding to these grounds of rejection, the claims as amended herewith are in compliance with the written description and enablement requirements of 35 U.S.C. §112, and are entitled to the earliest priority date (June 7, 2002). This is discussed in more detail below.

II. NEW MATTER

The amendment filed January 16, 2009 is objected to under 35 U.S.C. §132 as allegedly introducing new matter. In response, the reference to Lash *et al.* in the paragraph beginning at page 30, line 29 has been cancelled. Withdrawal of the new matter rejection is respectfully requested.

III. SPECIFICATION

The specification has been objected to because the reference to Triton at page 29 of the specification has not been marked as a trademark. In response, "Triton" has

been replaced by "Triton®". Withdrawal of the objection to the specification is respectfully requested.

IV. THE 35 U.S.C. §112, SECOND PARAGRAPH, REJECTION

Claims 1-3 and 6-10 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite. The rejection is respectfully traversed.

The Action asserts that claims 1-3 and 6-10 are unclear because the term "$sPLA_2$-IIA" is the sole means of identifying the polypeptides of the claims. The Action objects to the term "$sPLA_2$-IIA" as not clearly defining the polypeptide and alleges that the claims do not define the specific isoforms or activities of $sPLA_2$-IIA that are inhibited by the peptide inhibitors.

In response, and without conceding to the rejection, claims 2 and 6-9 have been cancelled without prejudice, and claim 1 has been amended to recite the specific $sPLA_2$-IIA polypeptide sequence (SEQ ID NO: 3) that is targeted by the inhibitors of the invention. Basis for this amendment appears at pages 10 and 11 of the specification and also in the originally filed sequence listing. The amended claims also specify that the activity that must be inhibited is the **enzyme activity** of the $sPLA_2$-IIA polypeptide as defined in SEQ ID NO: 3.

The number of claims has not been increased, and no new matter or new issues are raised. Entry of the requested amendments at this stage of prosecution is accordingly respectfully requested.

The Action further asserts that the claims do not clearly limit the prostate cancer cells to those that express $sPLA_2$-IIA. In response, and without conceding to this point,

the suggestion presented in the Action of amending the claims to direct them towards an inhibitor that "inhibits the $sPLA_2$-IIA-mediated proliferation of prostate cancer cells" has been adopted. Withdrawal of the 35 USC §112,second paragraph, rejection is respectfully requested.

V. THE FIRST 35 U.S.C. §112, FIRST PARAGRAPH, REJECTION

Claims 1-3 and 6-10 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to satisfy the written description requirement, because the polypeptides and inhibitors are only defined by their function and not by their structure. In response, and in order to expedite prosecution, claims 2 and 6-9 have been cancelled without prejudice, and the polypeptides are now defined with reference to specific sequences from the Sequence Listing. The inhibitors have been limited to those with a structure defined in original claim 9.

Claim 9 is rejected (see page 32 of the Office Action) because Church *et al.*, J. Biol. Chem, 2001 Aug 31; **276** (35): 33156-33164, allegedly describes analogs of the peptide first disclosed by Tseng *et al.* which lack the inhibitory action of the original peptide. In particular, the Action refers to peptides in Figure 1 of Church *et al.* (ALSYK and FLSYE) that were found to be inactive.

In response, the peptides highlighted in the Action are inactive and do **not** fall within the scope of the subject matter of previous claim 9 (now incorporated into amended claim 1). The subject matter of previous claim 9 is directed to peptides of the general sequence A1-A2-A3-A4-A5 (i.e., an aromatic amino acid at A1, an aliphatic hydrophobic amino acid (Leu or Ile) at A2, a polar uncharged amino acid (Ser or Thr) at

A3, an aromatic amino acid at A4 and a positively charged amino acid at A5). The peptides asserted not to work are therefore not within the scope of the present claims as amended. Withdrawal of the written description rejection is respectfully requested.

VI. THE SECOND 35 U.S.C. §112, FIRST PARAGRAPH, REJECTION

Claims 1-3 and 6-10 stand rejected under 35 U.S.C. §112, first paragraph, on alleged lack of enablement grounds, because there is no *in vivo* data to support the claims. The Action alleges that there is unpredictability in the art regarding *in vitro* studies.

In response, the abstract submitted with the previous response (Scott *et al.*; copy attached hereto) provides ample support for the cyclic peptide inhibitors cFLSYR and c(2Nap)LS(2Nap)R being effective *in vivo* in a mouse xenograft model. In support of this, attention is also directed to the attached detailed experimental data (entitled "Experimental Data Slides") which clearly show that the cyclic peptide inhibitors cFLSYR and c(2Nap)LS(2Nap)R are effective *in vivo* in a mouse xenograft model of androgen independent tumour growth **without** toxicity. Slide 4 shows that subcutaneous administration of c(2Nap)LS(2Nap)R (1 mg/kg) and cFLSYR (10 mg/kg) slows down tumour growth in a mouse xenograft model. Slide 10 shows that the cyclic peptide inhibitors slow tumour growth in mice on oral delivery at a thrice-weekly 1 mg/kg dosage of c(2Nap)LS(2Nap)R and at a daily 2 mg/kg dosage of cFLSYR. Slide 11 shows that the cyclic peptide inhibitors prolong survival in some animals past 6 months at the dosages specified in Slide 10. Slide 12 shows that **complete** tumour regression even occurs in some animals post-treatment with the cyclic peptide inhibitors. Slide 13

further shows that the peptides show no sign of short-term toxicity at thrice-weekly 10 mg/kg doses for both c(2Nap)LS(2Nap)R and cFLSYR, as measured by serum tissue enzyme levels.

The Action further asserts (page 33, paragraph 3) that Sved *et al.* discloses that c(2Nap)LS(2Nap)R and cFLSYR are effective *in vivo* in mice. However, Sved *et al.* discloses that c(2Nap)LS(2Nap)R at 1mg/kg and cFLSYR at 10 mg/kg slowed the rate of growth of tumours in *in vivo* mouse models (see, page 6938, last paragraph, to page 6939. paragraph 1).

The allegation that it is questionable (see page 33 of the Action) whether the compounds of the invention could be delivered to humans at a dose that is non-toxic, is purely speculative. Slide 13 of the attached detailed experimental data clearly shows that the cyclic peptide inhibitors show no sign of one month toxicity at thrice-weekly 10 mg/kg doses for both c(2Nap)LS(2Nap)R and cFLSYR, as measured by serum tissue enzyme levels.

The statement in the Action (page 33, paragraph 3) regarding the toxicity of the peptides is only partially true. cFLSYR was not toxic at 100μM (only c(2Nap)LS(2Nap)R was). However, this concentration is 4-5 orders of magnitude higher than the concentration the inventors have used to inhibit the growth of prostate cancer cells (see experimental data slides). The toxicity arguments in the Action are therefore irrelevant.

It is believed that it would have been routine experimentation, and well within the capability of a person skilled in the art, as of the filing date of the present application, to determine the optimal concentration/dosages suitable for human use based on *in vivo* mouse data. In support of this, attached is a copy of the Food and Drug Administration

(FDA) Guidelines that provides guidance on estimating Human Equivalent Doses (HED) from animal dosing (see, in particular, Table 1 which provides detailed guidelines for conversion of animal doses to HED). These guidelines provide detailed guidance on predicted doses for humans derived from animal data. A person skilled in the art as of the filing date of this case would have routinely used this information with a reasonable expectation of successfully predicting human dosages from animal data. To illustrate, the following scenario is proposed.

The mouse data shows that a daily 2mg/kg dose of cFLSYR slows tumour growth (see slide 10 of the attached detailed experimental data). By consulting the FDA Guidelines, a person skilled in the art could reasonably predict that this equates to a single 10mg daily tablet dose of cFLSYR in humans, which is an achievable and reasonable dose for humans.

The Action asserts that the specification is enabling only for the particularly described inhibitors cFLSYR and c(2Nap)LS(2Nap)R. This position is respectfully traversed.

The substitutions in the A1-A2-A3-A4-A5 peptide inhibitor now recited in amended claim 1 (i.e., an aromatic amino acid at A1, an aliphatic hydrophobic amino acid (Leu or Ile) at A2, a polar uncharged amino acid (Ser or Thr) at A3, an aromatic amino acid at A4 and a positively charged amino acid at A5) are structurally and functionally very conservative. A person of ordinary skill in the art could reasonably have predicted that these conservative substitutions would not significantly impact on the activity of the cyclic peptide in inhibiting prostate cancer cell proliferation.

Church *et al.* shows that a significant number of variants of the inhibitors of the peptides of the present invention inhibit $sPLA_2$-IIA in linear form (see Table 1 and discussion thereof). The structure-based design process used in Church *et al.* was guided by principles of protein chemistry that are well known to those in the art. Thus, it is well known that substitution of basic side chains (e.g., Arg for Lys), acidic side chains (Asp for Glu) and hydrophobic side chains (eg Phe for Leu) and aliphatic hydroxyl side chains (Ser for Thr) conserve structure and function. The quoted reference (Thwin *et al.*) supports rather than argues against the present inventors' approach, because a conservative substitution disclosed in Thwin *et al.* (Glu for Asp) retained inhibition activity while non-conservative substitutions (Ala or Ser for Asp) reduced inhibition significantly (see Thwin, p5939, end column 1 and start column 2).

The Action further alleges (page 33, paragraph 3) that there is no evidence of improvement of potency of FLSYK upon cyclization. To the contrary, attention is directed to page 33161, column 2, of Church *et al.* which states that:

> "Cyclisation of FLSYK (data not shown) or of the analogue FLSYR resulted in an improvement in potency of inhibition by 5-fold relative to linear FLSYK (Fig. 4A)..."

The present inventors have now shown that cyclisation of the FLSYR and (2Nap)LS(2Nap)R peptides enhances their inhibitory action in inhibiting prostate cancer cell proliferation. It therefore follows that a person skilled in the art could reasonably have predicted that cFLSYK would similarly enhance the inhibitory action of the peptide. The failure to observe inhibition on cyclisation in the case of Thwin *et al.* reflects the specific features of these peptides. Accordingly, the fact the present peptides improve

activity on cyclisation argues strongly that this feature will be retained for this class of inhibitor.

The Action asserts that the specification is enabling only for inhibition of the proliferation of two out of three prostate cancer cell lines tested (LNCaP and PC-3, but not DU-145 - page 14 and 25 of the Action). In response, LNCaP is an androgen-dependent cell line and PC-3 is an androgen-independent cell line, and both express $sPLA_2$-IIA. The compounds of the invention therefore work on both androgen-dependent and androgen-independent cancer cells that express $sPLA_2$-IIA. The claims are now limited to prostate cancer cells *that express $sPLA_2$-IIA of SEQ ID NO: 3*. It is well known in the art that DU-145 cells do not express $sPLA_2$-IIA. This is why the inhibitors of the present invention do not work on DU-145 cells. Furthermore, DU-145 cells are clonal and so not necessarily representative of prostate cancer.

In view of the above, it is clear that the *in vitro* data provided in the specification is predictive of the specific inhibitors of the specific $sPLA_2$-IIA sequence now claimed being effective *in vivo* and is enabling for the inhibitors as now claimed. Withdrawal of the lack of enablement rejection is respectfully requested.

VII. THE ANTICIPATION REJECTION

Claims 1-3 and 6-10 stand rejected under 35 U.S.C. §102(a) as allegedly anticipated by Sved *et al.* (Cancer Res. 2004 October 1; 64:6934-6940) (Sved). The rejection is respectfully traversed.

Sved (2004) was published after the priority date of the present application. For the reasons discussed above, the claims as amended clearly meet the written

description and enablement requirements and, as such, are entitled to their earliest priority date. Withdrawal of the anticipation rejection based on Sved is accordingly respectfully requested.

VIII. THE OBVIOUSNESS REJECTIONS

Claims 1-3 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Graff *et al.*, Clin. Cancer Res. 2001 Dec; **7**: 3857-3861 (Graff) in view of Attiga *et al.*, Cancer Res. 2000 Aug. 15; **60**: 4629-4637 (Attiga), Liu *et al.*, J. Urol. 2000 Sept; **164**: 820-825 (Lui) or Kelavkar *et al.*, Carcinogenesis, 2001 Nov; **22** (11): 1765-1773 (Kelavkar). Claims 6-10 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Graff in view of Attiga, Liu or Kelavkar and further in view of Church *et al.*, J. Biol. Chem, 2001 Aug 31; **276** (35): 33156-33164. The rejections are respectfully traversed.

In response, and without conceding to this rejections, claim 2 has been cancelled without prejudice, and claim 1 (upon which claim 3 is dependent) has been amended to recite specific amino acid sequences, and the inhibitors have been limited to those with a structure defined in original claim 9. Claim 9 has been canceled without prejudice.

The claims as amended now define the structure of the inhibitors, which is neither taught nor suggested by the cited prior art. Withdrawal of the obviousness rejection of claims 1-3 is respectfully requested.

Referring to the rejection of claims 6-10 as allegedly unpatentable over Attiga *et al.*, Liu *et al.* and Kelavkar *et al.* when combined with Graff *et al.* and further combined with Church *et al.*, claims 6-9 have been cancelled without prejudice and as noted

earlier, claim 1 has been amended to incorporate the subject matter of claim 9. Withdrawal of the obviousness rejection of claims 6-10 is respectfully requested.

The Action asserts that by combining Attiga *et al.*, Liu *et al.* and Kelavkar *et al.* (which respectively disclose that inhibition of a PLA_2 inhibitor, a general cyclooxygenase (COX) inhibitor, a COX-2 inhibitor and a lipooxygenase (LOX) inhibitor is useful in inhibiting the proliferation of prostate cancer cells), in light of Graff *et al.* (which discloses that $sPLA_2$-IIA is elevated in the serum of prostate cancer patients), it would allegedly have been obvious to a person skilled in the art to inhibit $sPLA_2$-IIA. This is not correct.

Graff discloses that $sPLA_2$-IIA is elevated in the *tissue* of prostate cancer patients. However, as argued in the prior response, the fact that an agent is elevated in tissue in a disease state does not necessarily indicate that inhibition of that agent will lead to an effective treatment. Furthermore, Graff provides no specific examples of inhibitors of $sPLA_2$-IIA that are suitable for treating prostate cancer. Graff therefore is not an enabling disclosure with regard to the presently claimed invention, and would have provided no motivation to a person skilled in the art to produce $sPLA_2$-IIA inhibitors which inhibit the $sPLA_2$-IIA-mediated proliferation of prostate cancer as now claimed.

Attiga *et al.*, Liu *et al.* and Kelavkar *et al.* disclose that inhibition of a PLA_2 inhibitor, a general cyclooxygenase (COX) inhibitor, a COX-2 inhibitor and a lipooxygenase (LOX) inhibitor, respectively, is useful in inhibiting the proliferation of prostate cancer cells. However, none of these references discloses a $sPLA_2$-IIA inhibitor as now claimed. It would not have been predictable to one of ordinary skill that inhibition of an upstream enzyme, for example a PLA2 enzyme, would have a similar

effect. Furthermore, since there are numerous PLA_2 enzymes (cytosolic and secreted isoforms), it would not have been obvious, based on Attiga *et al.*, Liu *et al.* or Kelavkar *et al.*, to target the specific $sPLA_2$-IIA polypeptide now claimed with a reasonable expectation of successfully inhibiting the sPLA2-IIA-mediated proliferation of prostate cancer. In this respect, attention is directed to Reid (2005) *Current Medicinal Chemistry* 12, 3011-3026 (copy attached), which discloses that:

> "there is considerable uncertainty about which PLA2 enzyme, or combination of enzymes, is responsible for arachidonic acid release" (see page 3013, second paragraph)...and that "studies have suggested that arachidonic acid production is very complex and involves more than a single PLA2 enzyme" (see page 3013, second paragraph).

Thus, even in 2005, years after the present application was filed, there remained considerable uncertainty in the art over the roles PLA_2 enzymes played in the eicosanoid biosythesis pathway. It would not therefore have been obvious to a person of ordinary skill in this art, upon reading Attiga *et al.*, Liu *et al.* and Kelavkar *et al.* (which relates to enzymes in the eicosanoid pathway *downstream* of $sPLA_2$-IIA), even in combination with Graff *et al.*, to produce the specific inhibitors of the specific $sPLA_2$-IIA polypeptide now claimed wherein the inhibitor inhibits the $sPLA_2$-IIA-mediated proliferation of prostate cancer cells.

The deficiencies of Attiga *et al.*, Liu *et al.*, Kelavkar *et al.* and Graff are not cured by Church *et al.*. Church *et al.* discloses compounds which are inhibitors of $sPLA_2$-IIA useful in regulation of *inflammatory responses*. However, there is no disclosure or suggestion in Church *et al.* that these compounds would be suitable for use as a treatment for *prostate cancer*. The inventive step made by the present inventors was

showing the functional importance of $sPLA_2$-IIA inhibition in prostate cancer cells expressing $sPLA_2$-IIA. The claims as amended are clearly non-obvious over the cited prior art, including Church *et al.*, which relates to regulation of *inflammatory responses* rather than a method of inhibiting or reducing the proliferation of *prostate cancer*, as presently claimed.

For all of the reasons presented above, the cited prior art fails to give rise to *prima facie* case of obviousness. Withdrawal of the obviousness rejections is respectfully requested.

Favorable action on this application is awaited.

Respectfully submitted,

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